NOVEL TARGETS FOR VOLUME OVERLOAD INDUCED LEFT VENTRICULAR HYPERTROPHY

Kamilla Gömöri[1,2], Éva Kenyeres[1], Tamara Szabados[1,3], Barna Váradi[4], Gergely Ágoston[5], Bence Ágg[3,4], Nazha Hamdani[2,4], István Leprán[1], Anikó Görbe[1,3,4], Péter Ferdinandy[3,4], Péter Bencsik[1,3]

[1]*Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary*
[2]*Institut für Forschung und Lehre (IFL), Molecular and Experimental Cardiology, Ruhr University Bochum, Bochum, Germany*
[3]*Pharmahungary Group, Szeged, Hungary*
[4]*Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary*
[5]*Institute of Family Medicine, University of Szeged, Szeged, Hungary;*

Volume overload (VO)-induced cardiac eccentric hypertrophy occurs in mitral or aortic valve regurgitation as well as during remodeling after myocardial ischemia. Although, anti-remodeling treatment is available, there is no specific treatment to stop or reverse cardiac hypertrophy. Therefore, our aim was to identify novel players in the development of VO-induced eccentric hypertrophy by using transcriptomics and bioinformatics. In this study, VO was induced by an aorto-caval fistula in 2-month-old male Wistar rats. Sham operated animals served as control. Functional parameters were measured by transthoracic echocardiography at termination, 4- or 8-months after induction of VO. We found hypertrophic remodeling, which was accompanied by mechanical dysfunction and increased cardiomyocyte stiffness. Total RNA was isolated from LV samples and microRNA deep sequencing was performed to identify altered microRNA profile. Via bioinformatic target prediction, mRNA targets possessing at least 4 connections to altered microRNAs were selected for further analyses. Out of 752 microRNAs being present in LV samples during deep sequencing, 22 microRNAs showed significant down- and 12 microRNAs significant up-regulation according both log2 fold-change and adjusted p value between the 8m-VO as compared to 8m-sham group. Bioinformatic target prediction by using microRNA-mRNA network analysis identified 3 mRNA targets, Nova1, Btg2 and Rock2 connected to 5 differentially expressed microRNAs as well as further 12 mRNAs possessing 4 connections to altered microRNAs. Biological validation of the results at mRNA and/or protein level is required, however, it seems that Nova1, Btg2 and Rock2 may play a pivotal role in the development of eccentric ventricular hypertrophy induced by VO.

Keywords: left ventricular eccentric hypertrophy, volume overload, aorto-caval fistula, microRNA profile, bioinformatic target prediction

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